wherein the particles consist of the stabilized peptide, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

Amendments to the claims are indicated in the attached "Marked Up Version of Amendments" (pages i - iii).

REMARKS

Claims 50, 63-66, 69, 91, 103-106 and 128-131 have been amended herein. Amended Claims 50, 69 and 91 are directed to a method for producing spray-dried particles having improved stability of a protein or peptide comprising combining a protein or peptide, a phospholipid and a co-solvent or an organic solvent and, optionally, a buffer salt, and spray drying the resulting mixture to produce spray-dried particles comprising a stabilized protein or peptide wherein the particles consist of the stabilized protein, or peptide, the phospholipid and, optionally, the buffer salt; and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent. In Claims 128-131 the buffer salt is required.

Claims 63-66 and 103-106 have been amended to correct improper dependencies inadvertently overlooked.

Support for amended Claims 50, 63-66, 69, 91, 103-106 and 128-131 is found throughout the specification and in the originally filed claims. No new matter has been introduced.

Rejection of Claims 50-69, 91-108 and 128-131 Under 35 U.S.C. § 103(a)

Claims 50-69, 91-108 and 128-131 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Durrani *et al.* ("Durrani").

In support of the rejection the Examiner states:

> One of ordinary skill in the art would have been motivated to make a spray dried composition of a drug and a lipid based on the generic claim of Durrani. The expected result would be a stable spray dried powder formulation. Therefore, this invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicants respectfully disagree. In addition to the arguments previously made, which are incorporated by reference herein in their entirety, Applicants would like to emphasize that the

present invention teaches methods for producing and administering spray-dried particles having properties and formulations neither disclosed nor suggested by Durrani.

Durrani is concerned with preparing drug/lipid powders which effectively form liposomes with high drug encapsulation upon rehydration of the dried powder particles (See page 4, lines 11-15). Durrani describes an improved method for direct spray-drying a drug/lipid composition to produce a powder which forms liposomes upon rehydration that is essentially equivalent to that achieved by previous methods of spray-drying a drug/lipid composition which required the ***preformation*** of a liposome encapsulated drug suspension prior to spray-drying the liposome encapsulated drug suspension. Durrani teaches that the improved method alleviates the prior art need to ***preform*** liposome encapsulated drug suspensions while producing equivalent powders, and goes on to describe the ingredients and steps required to produce such powders. Durrani is only concerned about generating a powder which, upon rehydration, yields liposome encapsulated drug at a comparable percent encapsulation to spray-dried preformed liposomes. Therefore, there is no motivation or suggestion to use the methods of Durrani to overcome the obstacles involved with the spray-drying of proteins or which would direct the ordinarily skilled artisan to modify the cited generic claim to reach Applicants' claimed invention.

All working examples presented in Durrani specifically teach particles which include, in addition to albuterol sulfate and lipid(s), other ingredients such as α- tocopherol, cholesterol and freon. Applicants note, for instance, the presence of the additional ingredient α-tocopherol, which at page 9, lines 20-21 is described as "a drug-protective and lipid-protective agent," in all formulations taught with specificity in the working examples of Durrani. Accordingly, Durrani teaches away from particles which do not need such ingredients as a "drug-protective and lipid-protective agent" as taught by Durrani.

As exemplified by Weiner *et al.* ("Liposomes as a Drug Delivery System", *Drug Development and Industrial Pharmacy*, 15(10): 1523-1554 (1989))(enclosed as Exhibit A), the production and use of liposomes as a drug delivery system is a complex and distinct art with its own unique concerns and obstacles. Weiner *et al.* describe the properties of liposomes, how liposomes are prepared and how they have been, and continue to be, adapted to efficiently and safely encapsulate a drug. Weiner *et al.* describe the various types of lipids that can be used to generate liposomes and the benefits and disadvantages of each. (see pages 1525-1529). Furthermore, Weiner *et al.* go on to state that "the internal or trapped volume and encapsulation efficiency greatly depends on liposomal content, lipid concentration, method of preparation and drug used." (see page 1532, last paragraph). Weiner *et al.* teach the importance of the role of

cholesterol in the formation of liposomes, the encapsulation of drugs and the resulting stability of the liposomes. (see page 1527, first paragraph). Moreover, Weiner *et al.* teach the various drug/liposomal interactions and how to calculate the encapsulation efficiency of the liposomes (e.g., the percent of the aqueous phase, and hence the percent of water soluble drug) that becomes entrapped during liposome preparation. (see page 1532, section: Internal Volume and Encapsulation Efficiency). The teachings of Weiner *et al.* are consistent with the teachings of Durrani. Durrani stresses the importance of the types of lipids used in the formulation and the addition of drug- and lipid-protective agents such as cholesterol and α-tocopherol.

Thus, Durrani includes in its particles additional ingredients which materially affect the basic and novel characteristics of the claimed invention. Applicants respectfully submit that Durrani does not teach, suggest or recognize the possibility of preparing spray dried particles comprising a stabilized protein (or peptide) which consists of the protein, phospholipid and, optionally, the buffer salt of the present claims.

As such, the claimed invention is non-obvious over the Durrani reference. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

50. (Thrice Amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid, a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, and, optionally, a buffer salt, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized protein;

wherein the particles consist [essentially] of the stabilized protein, the phospholipid and, optionally, the buffer salt, and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

63. (Amended) The method of Claim 50 [62] wherein the spray-dried particles have a tap density less than about 0.1 g/cm^3.

64. (Amended) The method of Claim 50 [63] wherein the spray-dried particles have a tap density less than about 0.05 g/cm^3.

65. (Amended) The method of Claim 50 [62] wherein the spray-dried particles have a median geometric diameter of between about 5 microns and about 30 microns.

66. (Amended) The method of Claim 50 [62] wherein the spray-dried particles have an aerodynamic diameter of between about 1 micron and about 5 micron.

69. (Thrice Amended) A method for producing spray-dried particles having improved stability of a peptide comprising:

(a) combining a peptide, a phospholipid, a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, and, optionally, a buffer salt, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized peptide;

wherein the particles consist [essentially] of the stabilized peptide, the phospholipid and, optionally, the buffer salt, and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

91. (Thrice Amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid, an organic solvent, and, optionally, a buffer salt, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized protein;

wherein the particles consist [essentially] of the stabilized protein, the phospholipid and, optionally, the buffer salt, and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

103. (Amended) The method of Claim 91 [102] wherein the spray-dried particles have a tap density less than about 0.1 g/cm^3.

104. (Amended) The method of Claim 91 [103] wherein the spray-dried particles have a tap density less than about 0.05 g/cm^3.

105. (Amended) The method of Claim 91 [102] wherein the spray-dried particles have a median geometric diameter of between about 5 microns and about 30 microns.

106. (Amended) The method of Claim 91 [102] wherein the spray-dried particles have an aerodynamic diameter of between about 1 micron and about 5 micron.

128. (Twice Amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid, a buffer salt and a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized protein;

wherein the particles consist [essentially] of the stabilized protein, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

129. (Twice Amended) A method for producing spray-dried particles having improved stability of a peptide comprising:

(a) combining a peptide, a phospholipid, a buffer salt and a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized peptide;

wherein the particles consist [essentially] of the stabilized peptide, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

130. (Twice Amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid, a buffer salt and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized protein;

wherein the particles consist [essentially] of the stabilized protein, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

131. (Twice Amended) A method for producing spray-dried particles having improved stability of a peptide comprising:

(a) combining a peptide, a phospholipid, a buffer salt and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized peptide;

wherein the particles consist [essentially] of the stabilized peptide, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.